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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,346	SOUSA ET AL.	
	Examiner	Art Unit	
	Arun Chakrabarti	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-62* is/are pending in the application.

4a) Of the above claim(s) *63-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Specification

1. Applicant's election of Group I, corresponding to claims 41-62, without traverse in Paper No: 8, is hereby acknowledged.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 41-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods using the T7 RNA polymerase with the Y639F and the SP6 Y631F RNA polymerase mutations does not reasonably provide enablement for any possible T7-type RNA polymerase with reduced discrimination for non-canonical versus canonical nucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Court in re Wands, 8 USPQ2d 1400 (CA FC 1988) stated with regard to enablement that

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Here, the claim is broadly drawn to any T7-type RNA polymerase which meets the test of incorporating both canonical and non-canonical nucleotides. However, the specification does not provide guidance commensurate in scope with this claim, teaching only two RNA polymerases which meets the requirement. The specification provides minimal guidance regarding methods for the isolation of additional mutations in RNA polymerases which meet this non-canonical use requirement. The specification also provides two working examples, which are represented by the T7 RNA polymerase with the Y639F mutation and SP6 with Y631F mutation. The cited prior art of Sousa (Embo Journal, (1995, Sep.15), Vol. 14 (18), pages 4609-21) shows that in a screening assay, only 1 out of 27 RNA polymerases were identified which had the reduced discriminatory phenotype. This demonstrates the unpredictability of the event, since Sousa was testing RNA polymerases with active site mutations, and found only a single enzyme with the desired function. Further evidence, from the prior art of the unpredictability of

the invention is provided by Kostyuk et al (FEBS Letters, (1995), Vol. 369, 165-168) who states, "we have generated mutant enzymes with phenylalanine in place of tyrosine at position 639, alanine in place of serine in position 641 and a double mutant bearing both of these substitutions. The substrate specificity and other features of the latter two proteins were found to be quite surprising." Kostyuk's express statement that the substrate specicity was "surprising" expressly demonstrates the unpredictable nature of these results. While the skill level in the art is high, it is therefore highly unpredictable whether other RNA polymerases can be identified which meets this specific criteria regarding the use of non-canonical nucleotides. Further, identification of additional mutations will be by the trial and error method. This trial and error requirement is borne out because protein structural effects caused by mutations cannot be readily deduced, even where the crystallographic structures are known. Further, each mutation has unpredictable effects on protein function, and no general method for a priori selection of functional mutations is presented. It would require a large amount of experimentation, potentially including the synthesis of hundreds of mutations, in order to identify additional polymerases with the claimed functionality. Given the Wand's factors opposing the full scope of enablement including the limited teaching in the specification, the presence of only two working examples, the teaching of unpredictability in the prior art, the unpredictability of the art, the breadth of the claim, and the large amount of experimentation needed, with only the skill level in the art supporting enablement, it is concluded that undue experimentation is necessary to make and use the invention as broadly claimed.

3. Claims 41-45 and 55-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the phrase "*de novo*" in claims 41, 55 and other claims. "De novo" means starting from scratch or nothing. Because RNA polymerase molecules require a template in order to polymerize nucleic acids, it is unclear what limitation is imposed by the term "de novo". That is, it is indefinite whether "de novo" simply refers to the synthesis of a new strand using a template, or if some novel, template free method is intended. It is suggested that this term be changed to clarify what is meant.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CAR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CAR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CAR 3.73(b).

5. Claims 41, 43-46, 48-55, and 57-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,107,037. Although the conflicting claims are not identical, they are not patentably distinct from each other because species (mutation of T7 RNA polymerase at position 639) claimed in U.S. Patent No. 6,107,037 anticipates the genus of instant claims i.e, any mutation of T7 RNA polymerase.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 41-54 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Axelrod et al (Biochemistry (1985) 24:5716-5723) in view of Sousa et al (Embo Journal, (1995, Sep.15), Vol. 14 (18), pages 4609-21) and further in view of Innis et al (U.S. Patent 5,075,216).

Axelrod teaches method for determining the sequence of a nucleic acid molecule using an RNA polymerase (abstract) comprising the steps:

a) synthesizing a nucleic acid molecule from an RNA polymerase promoter in a reaction mixture containing an RNA polymerase in each of four separate reactions, each reaction

comprising at least four nucleoside triphosphates, wherein at least each of A, C, G and U are used and a different chain terminator in each reaction, and

b) evaluating the reaction products so that the sequence of the template molecule may be deduced (page 5718, particularly figure 3).

Axelrod does not teach substitution of wild type RNA polymerase with a mutant RNA polymerase which has reduced discrimination for non-canonical versus canonical nucleotide as substrates. Axelrod does not teach use of ddNTP or fluorescently labeled nucleotides.

Sousa teaches the use of an RNA polymerase which has reduced discrimination between canonical and non-canonical nucleoside triphosphates (page 4614, table II).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the RNA polymerase of Sousa into the sequencing method of Axelrod since Sousa motivates the use of the mutant T7 RNA polymerase noting, "Depending on the substrates and templates presented to it, the Y639F T7 RNAP can act as an RNA- or DNA- directed RNA or DNA polymerase in primed or de novo initiated reactions. Thus it can display a variety of activities normally associated with distinct polymerases, including some entirely novel activities, such as de novo initiated reverse transcription or mixed dNMP/rNMP polymer synthesis (Page 4620)." An ordinary practitioner would have been motivated to substitute the RNA polymerase of Sousa into the sequencing method of Axelrod to permit selection of a wider use of nucleotide analogues and enhance efficiency of the sequencing reaction.

Axelrod in view of Sousa do not teach DNA sequencing using ddNTPs and fluorescently labeled nucleotides.

Innis teaches DNA sequencing using ddNTPs and fluorescently labeled nucleotides (columns 1 and 5 and column 8, lines 23-44).

It would further have been prima facie obvious to substitute the use of ddNTPs and fluorescent as taught by Innis into the sequencing method since Innis notes "The present invention also encompasses a variety of methods for incorporating labeled nucleotide during the sequencing reaction (column 8, lines 23-25)". Innis continues a few lines later, "Another method involves incorporation of a labeled nucleotide into the extending primer (column 8, lines 27-29)". Innis expressly notes the use of ddNTP terminators (column 5, lines 40-59). An ordinary practitioner would have been motivated to use the terminators and fluorescent nucleotides of Innis in the method of Axelrod in view of Sousa in order to use more widely available kits which contain ddNTPs and to minimize costs by using widely available ddNTP sequencing methods.

8. Claims 55, 56, 57, 60, 61 and 62 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Koster et al (U.S. Patent 5,622,824) in view of Sousa et al (Embo Journal, (1995, Sep.15), Vol. 14 (18), pages 4609-21).

Koster teaches method for determining the sequence of a nucleic acid molecule using an RNA polymerase (column 10) comprising the steps:

a) synthesizing a nucleic acid molecule from an RNA polymerase promoter in a reaction mixture containing an RNA polymerase, the reaction comprising at least four nucleoside

triphosphates, wherein at least each of A, C, G and U are used (column 10), and in which four separate reactions are performed (column 18, lines 15-21) and

b) treating the nucleic acid products with an exonuclease to cleave the ribonucleotides (column 10)

c) evaluating the reaction products so that the sequence of the template molecule may be deduced (column 10).

Koster does not teach substitution of wild type RNA polymerase with a mutant RNA polymerase which has reduced discrimination for non-canonical versus canonical nucleotide as substrates.

Sousa teaches the use of an RNA polymerase which has reduced discrimination between canonical and non-canonical nucleoside triphosphates (page 4614, table II).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the RNA polymerase of Sousa into the sequencing method of Koster since Sousa motivates the use of the mutant T7 RNA polymerase noting, "Depending on the substrates and templates presented to it, the Y639F T7 RNAP can act as an RNA- or DNA- directed RNA or DNA polymerase in primed or de novo initiated reactions. Thus it can display a variety of activities normally associated with distinct polymerases, including some entirely novel activities, such as de novo initiated reverse transcription or mixed dNMP/rNMP polymer synthesis (Page 4620)." An ordinary practitioner would have been motivated to substitute the RNA polymerase of Sousa into the sequencing method of Koster to permit

selection of a wider use of nucleotide analogues including more efficient incorporation of the mass labeled rNTPs and enhance efficiency of the sequencing reaction.

9. Claims 58, and 59 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Sousa et al (Embo Journal, (1995, Sep.15), Vol. 14 (18), pages 4609-21) in view of Stratagene Catalog (1988, page 39).

Sousa teaches the use of an RNA polymerase which has reduced discrimination between canonical and non-canonical nucleoside triphosphates (page 4614, table II). With regard to the preamble limitations, it is noted in MPEP 2111.02 that "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Here, the intended use in various methods imposes no structural constraints upon the kit.

Sousa does not teach placement of the RNA polymerase reagent into a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the RNA polymerase of Sousa into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram

amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

10. Claims 58, and 59 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kostyuk et al (FEBS Lett. (1995) 369:165-168) in view of Stratagene Catalog (1988, page 39).

Kostyuk teaches the use of an RNA polymerase which has reduced discrimination between canonical and non-canonical nucleoside triphosphates (page 166, figure 2). With regard to the preamble limitations, it is noted in MPEP 2111.02 that "a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Here, the intended use in various methods imposes no structural constraints upon the kit.

Kostyuk does not teach placement of the RNA polymerase reagent into a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the RNA polymerase of Kostyuk into a kit format as

discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti

Patent Examiner,

April 22, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER